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MINIREVIEW

Properties and Mechanisms of Long-Term Synaptic Plasticity in the Mammalian Brain: Relationships to Learning and Memory

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Long-term potentiation (LTP) in the hippocampus and long-term depression (LTD) in the cerebellum are two forms of long-lasting synaptic plasticity that currently serve as our primary experimental models of learning and memory formation in mammals. In recent years, there have been considerable advances in our understanding of the cellular and molecular mechanisms of these and other forms of synaptic plasticity. This article presents an overview of these developments, considers the relationship of long-term synaptic plasticity mechanisms to learning and memory in view of these developments, and suggests future directions for research in this rapidly growing area of neuroscience.

In his now classic book, "The Organization of Behavior" (1949), Donald Hebb proposed that memories are stored in the mammalian brain as stronger synaptic connections between neurons active during learning. The specific mechanism he suggested to bring about these changes in synaptic transmission is relatively simple. Hebb postulated that increments in synaptic efficacy occur during learning when firing of one neuron repeatedly produces firing in another neuron to which it is connected. In other words, correlation (or association) of pre- and postsynaptic activity in two neurons elicits some change in one or both of the neurons such that the synaptic connection between them is strengthened (Hebb, 1949). We will refer to synapses that are modified in this manner as "Hebbian synapses" or "Hebb synapses." Hebb's proposal that memory depends on the coactivity of neural elements was not a new one; it had been expressed in various forms by many earlier authors.[2] However, it was not until the publication of Hebb's book that a specific *synaptic* mechanism had been proposed for the formation of memory at *extant* neuronal connections. The importance of Hebb's contribution in this regard cannot be contested: the Hebb synapse is a construct that has become a theoretical foundation for many neurobiological and computational models of synaptic plasticity and has revolutionized thinking about the nature of the neural mechanisms of learning and memory formation.

In the years since the publication of Hebb's book, a growing body of evidence has emerged supporting the view that memories are represented as enduring changes in the functional circuitry of the brain and that synaptic contacts between neurons serve as the pliable substrate for "memory traces." Perhaps most important in this regard was the discovery by Bliss, Gardner-Medwin, and Lømo in 1973 of a long-lasting increase in synaptic efficacy following electrical stimulation of the rabbit hippocampus (Bliss & Gardner-Medwin, 1973; Bliss & Lømo, 1973). This

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[2] Similar ideas can be traced back to the much earlier writings of Sir Charles Bonnett (1720–1793), who held that memories were represented in the brain by use-dependent changes in the "resonance threshold" of nerves (for a historical review of thought concerning the mechanisms of memory see Gomulicki, 1953).

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form of long-term synaptic plasticity, known as long-term potentiation or LTP, is induced by correlated pre- and postsynaptic activity (i.e., it is Hebbian) and exhibits several properties typical of learning and memory (for reviews see Bliss & Collingridge, 1993, and Teyler & DiScenna, 1984). More recently, Masao Ito and colleagues have identified a similar but distinct form of synaptic plasticity in the cerebellum known as long-term depression or LTD (for a review see Ito, 1989). These investigators found that electrical stimulation of the cerebellum produced a long-lasting decrement in synaptic efficacy. Like hippocampal LTP, cerebellar LTD is Hebbian and exhibits properties typical of memory (Ito, 1989). Because both the hippocampus (Zola-Morgan & Squire, 1990) and the cerebellum (Thompson, 1990) are important for various forms of learning and memory in mammals, hippocampal LTP and cerebellar LTD are considered strong candidates for cellular mechanisms of memory formation.

In recent years, an impressive research effort has been devoted to understanding the cellular and molecular mechanisms of various forms of synaptic plasticity, particularly LTP in the hippocampus and LTD in the cerebellum. The aims of this article are (i) to present an overview of what is currently known about their cellular mechanisms and of molecular processes that may be common to many forms of synaptic plasticity and (ii) to discuss how the knowledge of cellular and molecular mechanisms of synaptic plasticity can provide a better understanding of the problem of learning and memory formation. Because this article is not intended to be a comprehensive review of the literature concerning the cellular and molecular mechanisms of synaptic plasticity and their relationship to learning and memory, the reader will be referred to more comprehensive reviews where necessary.

FORMS AND PROPERTIES OF MAMMALIAN SYNAPTIC PLASTICITY

In several brain structures, explicitly correlated pre- and postsynaptic neuronal activity results in either long-term increases (e.g., LTP) or long-term decreases (e.g., LTD) in synaptic efficacy (Nadel, Cooper, Culicover, & Harnish, 1989).[3] Both LTP and LTD have been reported in several brain structures including the hippocampus (Bliss & Lømo, 1973; Dudek & Bear, 1992; Mulkey & Malenka, 1992), amygdala (Chapman, Kairiss, Keenan, & Brown, 1990; Clugnet & LeDoux, 1990), and neocortex (Artola, Broecher, & Singer, 1990; Artola & Singer, 1993; Hirsch & Crepel, 1990; Laroche, Jay, & Thierry, 1990; Racine, Milgram, & Hafner, 1983). That many neural systems are capable of exhibiting long-term synaptic plasticity is consistent with the emerging view that there are multiple memory systems in the brain (e.g., Macdonald & White, 1993; Squire, 1992). However, the most intensively studied forms of Hebbian plasticity are LTP in the hippocampus and LTD in the cerebellar cortex, both of which result from coincident pre- and postsynaptic activity. These long-term forms of activity-dependent synaptic plasticity can be distinguished from less enduring forms of synaptic plasticity such as short-term potentiation (STP) and post-tetanic potentiation (PTP), which appear to be mediated by different cellular mechanisms (Bliss & Collingridge, 1993). The latter persist for minutes following induction, compared to hours or even days for the long-term forms of synaptic plasticity. For reasons discussed below, long-term synaptic plasticity mechanisms, particularly hippocampal LTP and cerebellar LTD, have generated a great deal of interest as putative cellular memory mechanisms. As a result, a considerable amount of research has been directed toward understanding the synaptic and molecular mechanisms of hippocampal LTP and cerebellar LTD and the relationship of these forms of synaptic plasticity to behavioral learning and memory.

Mechanisms of LTP Induction in Hippocampus

As a first approximation, hippocampal LTP follows Hebbian rules because it is induced by pairing presynaptic activity with postsynaptic depolarization (Brown, Kairiss, & Keenan, 1990).[4] In general, LTP induction in the hippocampus is accomplished by applying brief trains of rhythmic high-frequency stimulation to excitatory axons that project to hippocampal neurons.[5] Once induced, LTP is expressed as a persistent and synapse-specific increase in the

[3] Explicitly anti-correlated pre- and postsynaptic neuronal activity has been reported to decrease synaptic efficacy in the hippocampus (Stanton & Sejnowski, 1989); however, there have been several failures to replicate this result (e.g., Paulsen, Li, Hvalby, Andersen, & Bliss, 1993).

[4] Some more subtle aspects of LTP induction follow non-Hebbian rules. For example, maximal LTP is not always correlated with maximal postsynaptic depolarization (for further discussion of this point see Larson & Lynch, 1989).

[5] All three major excitatory pathways of the hippocampus support LTP. These consist of axonal projections from the entorhinal cortex to the dentate gyrus (perforant path), dentate gyrus to area CA3 (mossy fibers), and area CA3 to area CA1 (Schaffer collaterals).

amplitude of synaptic responses elicited by low-frequency stimulation of the excitatory afferents. Under normal conditions, hippocampal synaptic responses elicited by low-frequency stimulation are mediated primarily by the interaction of the excitatory neurotransmitter glutamate with α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptors, an ionotropic subclass of glutamate receptors that gates a fast cationic (Na^+,K^+) conductance (Collingridge, Kehl, & McLennan, 1983; Kauer, Malenka, & Nicoll, 1988; Muller, Joly, & Lynch, 1988). However, during high-frequency stimulation of excitatory afferents strong postsynaptic depolarization coupled with presynaptic glutamate release results in the activation of *N*-methyl-D-aspartate (NMDA) receptors by releasing the voltage-dependent Mg^{2+} blockade of their associated ionic channels (Mayer, Westbrook, & Guthrie, 1984; Nowak, Bregestovski, Ascher, Herbet, & Prochiantz, 1984).[6] NMDA receptor activation results in Ca^{2+} influx into postsynaptic structures (MacDermott, Mayer, Westbrook, Smith, & Barker, 1986), which triggers a series of enzymatic cascades that lead to a persistent modification of synaptic efficacy. The nature of these cascades is still poorly understood, but there is evidence for the involvement of protein kinases [protein kinase C (PKC), calcium-calmodulin kinase II (CamKII)], proteases (calpain), and phospholipases (phospholipase A_2; for a review see Massicotte & Baudry, 1990). Manipulations that prevent NMDA receptor activation such as postsynaptic hyperpolarization (Malinow & Miller, 1986), application of NMDA receptor antagonists (Collingridge et al., 1983; Maren, Baudry, & Thompson, 1991, 1992; Morris, Anderson, Lynch, & Baudry, 1986), or intracellular injections of Ca^{2+} chelators (Lynch, Larson, Kelso, Barrionuevo, & Schottler, 1983; Malenka, Kauer, Zucker, & Nicoll, 1988) prevent LTP induction. Furthermore, inhibitors of PKC and CamKII prevent the induction of LTP (Muller, Buchs, Dunant, & Lynch, 1990; Malinow, Schulman, & Tsien, 1989). Recent research indicates that another subclass of glutamate receptors, the glutamate metabotropic receptors (mGluRs), may also be required for LTP induction (Bashir, Bartolotto, Davies, Beretta, Irving, Seal, Henley, Jane, Watkins, & Collingridge, 1993; Riedel & Reymann, 1993); however, further study is required to understand the precise role mGluRs play in LTP.

The nature of the synaptic modification that expresses and maintains hippocampal LTP is a matter of controversy (for opposing views see Baudry & Davis, 1991). Currently, there is evidence for both presynaptic increases in neurotransmitter (glutamate) release (Bekkers & Stevens, 1990; Bliss, Clements, Errington, Lynch, & Williams, 1990; Malinow, 1991; Malgaroli & Tsien, 1992; Malinow & Tsien, 1990; O'Dell, Hawkins, Kandel, & Arancio, 1991; Schuman & Madison, 1991) and postsynaptic changes in glutamate (AMPA) receptors (Ambros-Ingerson, Larson, Xiao, & Lynch, 1991; Davies, Lester, Reymann, & Collingridge, 1989; Foster & McNaughton, 1991; Kauer et al., 1988; Manabe, Renner, & Nicoll, 1992; Maren et al., 1992; Maren, Tocco, Standley, Baudry, & Thompson, 1993b; Muller et al., 1988; Shahi & Baudry, 1992; Tocco, Maren, Shors, Baudry, & Thompson, 1992; Staubli, Ambros-Ingerson, & Lynch, 1992; Staubli, Kessler, & Lynch, 1990a; Xiao, Staubli, Kessler, & Lynch, 1991b) following hippocampal LTP induction. Another possibility is that LTP expression is mediated by a structural modification of the synapse, possibly involving transmembrane proteins such as integrins (Staubli, Vanderklish, & Lynch, 1990; Xiao, Bahr, Staubli, Vanderklish, & Lynch, 1991a; Wallace, Hawrylak, & Greenough, 1991). Ultimately, LTP expression is probably mediated by parallel changes in both pre- and postsynaptic loci; the critical issue for future studies is to understand the dynamics of these changes in relation to learning and memory.

Properties of Hippocampal LTP

Hippocampal LTP is a hallmark example of Hebbian synaptic plasticity; coincident pre- and postsynaptic activity yield a persistent increase in the efficacy of synaptic transmission. As is apparent from the discussion above, the Hebbian nature of LTP emerges from the specific activation requirements of NMDA receptors. That is, NMDA receptor activation, which we have seen is a prerequisite for LTP induction, occurs only under conditions of coincident presynaptic activity and postsynaptic depolarization. This Hebbian requirement for LTP induction provides the foundation for an important empirical property that both LTP and memory share: associativity. To illustrate associativity of LTP, Tom Brown and colleagues have shown that synaptic activity in a "weak" afferent pathway that

[6] Not all forms of LTP are dependent on NMDA receptor activation. Notably, LTP induction at mossy fiber synapses in hippocampal area CA3 (Staubli, Larson, & Lynch, 1990b; Zalutsky & Nicoll, 1990) and, under some conditions, LTP induction at Schaffer collateral synapses in hippocampal area CA1 (Grover & Teyler, 1990) do not require NMDA receptor activation. In this report, the focus will be restricted to NMDA receptor-dependent forms of LTP.

is unable to support LTP can be made to do so if paired (associated) with synaptic activity in a "strong" pathway that is able to produce LTP independently (Brown et al., 1990; Kelso, Ganong, & Brown, 1986). The failure of the weak pathway to support LTP when stimulated alone is due to insufficient (subthreshold) postsynaptic depolarization generated by stimulation and a consequent failure of stimulation to activate NMDA receptors. However, when activity in the weak pathway is paired with postsynaptic depolarization provided by stimulation of the strong pathway, NMDA receptors at the weak synapses are activated and LTP is induced. Experimentally, the level of postsynaptic depolarization required for LTP induction is only satisfied when a sufficient number of afferent fibers and synapses are activated, a property known as cooperativity (McNaughton, Douglas, & Goddard, 1978). The associative property of LTP is perhaps one of its most important because it can be used to explain various forms of learning. For example, during Pavlovian (classical) conditioning an initially neutral conditioned stimulus (CS; i.e., the weak pathway) comes to elicit a conditioned response (CR) similar to the unconditioned response (UR) elicited by an initially nonneutral unconditioned stimulus (US; i.e., the strong pathway). In this example, depolarization generated by the strong US pathway promotes NMDA receptor activation and LTP in the weaker CS pathway, which consequently becomes a potentiated CR pathway. As predicted from this model and as will be discussed in more detail in a later section, a number of manipulations that prevent NMDA receptor activation or postsynaptic depolarization interfere with learning. These phenomena provide strong support for involvement of LTP in learning and memory.

Hippocampal LTP exhibits many other properties typical of memory. For example, LTP is rapidly induced (it reaches a steady-state in less than 10 min following induction) and once stabilized it is quite resistant to disruption. For instance, hippocampal LTP induced *in vivo* persists from hours to several weeks depending on the induction parameters and stimulated pathways (Barnes, 1979; Staubli & Lynch, 1987). In addition, prior to stabilizing, LTP formation can be disrupted by a variety of manipulations such as hypoxia (Arai, Larson, & Lynch, 1990), electroconvulsive shock (ECS), or seizure activity (Hesse & Teyler, 1976; Massicotte, Vanderklish, Lynch, & Baudry, 1991), trains of low frequency or "depotentiating" stimuli (Fujii, Saito, Miyakawa, Ito, & Kato, 1991; Staubli & Lynch, 1990), and cooling shocks (Muller, Fukunaga, & Miyamoto, 1994). The vulnerability of LTP to disruption suggests a possible basis for the consolidation period frequently observed in behavioral studies of learning and memory (Kim & Fanselow, 1992; McGaugh, 1989; Zola-Morgan & Squire, 1990). Further support for a role for LTP in memory is indicated by the high correspondence between optimal LTP induction conditions and endogenous patterns of neural activity that accompany learning. Specifically, LTP is induced optimally by afferent stimulation that is patterned at theta frequency (4–12 Hz; Larson & Lynch, 1986), a frequency band that dominates the hippocampal EEG during information-gathering behaviors such as exploration in rats (Vanderwolf, 1969). Theta frequency stimulation is optimal for LTP induction because it facilitates $GABA_B$ autoreceptor-mediated depression of inhibitory interneurons, thereby opening a time-window for the postsynaptic target to sufficiently depolarize and activate NMDA receptors (Mott & Lewis, 1991). Thus, the hippocampal network seems to be particularly fine-tuned to exhibit maximal synaptic plasticity when global activity emerges in the theta range, a phenomenon that occurs during learning.

Mechanisms of LTD Induction in Cerebellum

Like LTP, LTD in the cerebellar cortex is a widely studied form of synaptic plasticity in the mammalian brain (for a review see Ito, 1989). LTD can be induced either by pairing low-frequency activity in parallel fibers (PFs) and climbing fibers (CFs; two excitatory afferent pathways that converge on cerebellar cortical Purkinje cells; Ito, 1989) or by pairing PF activity with direct Purkinje cell hyperpolarization (Crepel & Jaillard, 1991). The timing of PF and CF stimulation is critical; optimal LTD occurs when PF and CF activation are simultaneous. Following several pairings of PF and CF stimulation, synaptic responses in the PF pathway exhibit a marked and enduring depression. As in the hippocampus, fast excitatory synaptic transmission at both PF and CF synapses is mediated primarily by postsynaptic AMPA receptors (Crepel, Dupont, & Gardette, 1983; Perkel, Hestrin, Sah, & Nicoll, 1990). But unlike LTP induction, the critical events in LTD induction involve the coupling of a potent Ca^{2+} signal generated by CF discharges with activation of mGluRs at parallel fiber–Purkinje cell synapses. Thus, cerebellar LTD does not involve NMDA receptor activation (in fact, adult Purkinje cells lack NMDA receptors), but an increase in intracellular Ca^{2+} in postsynaptic Purkinje cells is

required (Sakurai, 1988). This elevation in intracellular Ca^{2+} is probably mediated by both voltage-gated Ca^{2+} channels activated by CF depolarization and the liberation of intracellular Ca^{2+} stores by a metabotropic receptor-mediated second messenger cascade (Okamoto & Sekiguchi, 1991). The modification that expresses LTD at PF synapses appears to be a sustained desensitization of AMPA receptor responses (Ito, Sakurai, & Tongroach, 1982; Kano & Kato, 1988; Linden, Dickinson, Smeyne, & Connor, 1991). Thus, the final common pathway for the induction and expression of both hippocampal LTP and cerebellar LTD is an elevation of intracellular Ca^{2+}, an activation of enzymatic cascades, and a modification of postsynaptic AMPA receptors. A similar cascade of events might also be responsible for LTP and LTD induction in other brain structures such as the neocortex and hippocampus, respectively.[7]

Properties of Cerebellar LTD

Cerebellar LTD shares many of the memory-like properties that hippocampal LTP exhibits. LTD is long-lasting (it has been observed to last for hours in *in vivo* preparations; Ito, 1989) and specific to stimulated synapses (i.e., PFs that are not paired with climbing fiber stimulation do not show LTD). Moreover, cerebellar LTD induction obeys Hebbian rules. In this case, Hebbian requirements are fulfilled by the strong postsynaptic depolarization generated by CFs in combination with presynaptic neurotransmitter release at PF–Purkinje cell synapses. As one might infer from the properties of LTP, the Hebbian nature of LTD also provides for associativity. Together, these properties are suggestive of a role for cerebellar LTD in learning and memory. However, one potential problem for a role for cerebellar LTD in learning is the lack of correspondence between optimal LTD induction parameters and optimal learning parameters in cerebellum-dependent tasks. For example, one form of learning that may depend on cerebellar LTD is classical eyeblink conditioning in rabbits. In this paradigm, an auditory CS precedes a corneal air puff US. After several pairings, the CS comes to elicit an eyeblink CR. Cerebellar cortical damage severely impairs both the acquisition and retention of this learned response, a consequence of disrupting one of the primary sites for convergence of CS and US information (CS and US information are conveyed to cerebellar cortex by PFs and CFs, respectively). Optimal eyeblink conditioning occurs with a CS–US interval of 250 ms, whereas LTD induction is apparently optimal when PF and CF discharge is simultaneous. However, further examination of the temporal parameters for LTD induction has revealed that a 250-ms PF–CF interval produces robust LTD in the cerebellum (C. Chen and R. F. Thompson, personal communication). Apparently, there is not a disparity between the temporal parameters for LTD induction and eyeblink conditioning. Collectively, these data are consistent with a role for cerebellar LTD in some forms of learning and memory.

MOLECULAR ANALYSES OF SYNAPTIC PLASTICITY

As discussed above, cellular analyses of synaptic plasticity in the CNS have revealed that modifications of synaptic efficacy follow generalized Hebbian or anti-Hebbian rules, i.e., simultaneous pre- and postsynaptic activity results in either increase or decrease in synaptic efficacy, whereas independent pre- or postsynaptic activity results in no change or decrease in synaptic efficacy. These phenomena imply the existence of sets of molecular devices capable of incorporating information related to pre- and postsynaptic activity. For many years, it was assumed that these devices had to be located in the postsynaptic neuron in order to compute order, time delays, and frequencies of different neural events converging on the same postsynaptic target; these devices would in turn trigger a modification of some critical elements regulating the strength of synaptic transmission (Finkel & Edelman, 1985; Heidmann & Changeux, 1982). However, recent evidence obtained from a variety of biological systems has suggested the existence of retrograde messengers, thus enlarging the spatial domain (e.g., Schuman & Madison, 1994) and the nature of potential molecular devices capable of integrating pre- and postsynaptic information. These cascades of biochemical mechanisms have to accomplish two separate objectives: (i) they have to capture all of the information related to the features of pre- and postsynaptic activity and

[7] Like cerebellar LTD, neocortical LTD induction does not require NMDA receptor activation (Artola et al., 1990; Hirsch & Crepel, 1991) and may be mediated by similar expression mechanisms. However, recent data indicate that LTD induction in the hippocampus, like LTP induction, does require NMDA receptor activation (Dudek & Bear, 1992; Mulkey & Malenka, 1992). Lest we conclude hippocampal LTD is distinct from LTD in other brain regions, it is important to note that hippocampal LTD is not readily induced in adult brain. Indeed, there is some reason to believe that hippocampal LTD may be an early ontogenetic manifestation of what later becomes a depotentiation mechanism in adult animals.

(ii) they have to produce long-lasting modifications in synaptic efficacy or, at least, they have to appropriately trigger another sequence of processes that could lead to such modifications. As a first approximation, changes in synaptic strength can result from either a change in transmitter release, a change in postsynaptic responses elicited by the transmitter or a combination of both changes. Research in the last 5 years has generated considerable information concerning all these different aspects, including the types of molecular devices integrating multiple signals, possible retrograde messengers, and the mechanisms regulating transmitter release and transmitter responsiveness.

Devices Integrating Pre- and Postsynaptic Activity

It is now clear that neurotransmitters have multiple receptors that generate a variety of cellular responses when they are activated. Two broad classes of receptors have been defined based on the type of signaling mechanism receptor activation triggers: (i) ionotropic receptors directly gate ionic channels and mediate fast signal transmission (milliseconds; Nicoll, 1988) and (ii) metabotropic receptors indirectly modify the activity of ionic channels through second messenger-mediated cascades of intracellular enzymatic activities and mediate slower signal transmission (from seconds to minutes or even hours; Berridge, 1987). Second messengers include Ca^{2+}, cyclic AMP, cyclic GMP, and a variety of phospholipid degradation products such as inositol triphosphate (IP_3) and arachidonic acid. One of the most important roles of second messengers is to regulate phosphorylation reactions, which serve as cellular integration devices. Phosphorylation reactions that modify ionic channels, neurotransmitter receptors, or synaptic proteins involved in the regulation of transmitter release are potential candidates for producing at least short-term regulation of synaptic efficacy (Goelet, Castellucci, Schacher, & Kandel, 1986; Hemmings, Nairn, McGuinness, Huganir, & Greengard, 1989). More complex reactions linking enzymatic cascades to structural modifications of synaptic contacts are probably necessary to produce long-lasting modification of synaptic transmission (see below). Finally, phosphorylation of transcription factors may allow second messenger-mediated genomic regulation of the expression of specific proteins (Morgan & Curran, 1991).

A major difficulty that these intracellular integration mechanisms have to resolve is the question of synaptic selectivity, a critical feature of activity-dependent modifications of synaptic efficacy. The substantial isolation of spine compartments from the main dendritic compartment in neurons with large dendritic trees and numerous spine synapses represents a serious problem for the integration of spatially distal events (Coss & Perkel, 1985). Nevertheless, several mechanisms are likely to contribute to the spatial propagation of electrical and chemical signals throughout the postsynaptic neuron. For instance, both the rapid diffusion of second messengers into the dendritic compartment (Finkel, Reeke, & Edelman, 1989) and the active propagation of membrane potential changes along the dendritic membrane constitute signaling mechanisms that incorporate spatial information. However, it remains more difficult to account for the synaptic selectivity mechanisms involving genomic responses.

Retrograde Messengers

Two major candidates have recently emerged as potential retrograde messengers providing presynaptic terminals information related to postsynaptic activity. The first, arachidonic acid, is generated from the degradation of membrane phospholipids by phospholipase A_2, a calcium-dependent enzyme (Bliss et al., 1990). The second, nitric oxide (NO), is a rapidly diffusible gas produced by Ca^{2+}–calmodulin activated nitric oxide synthase (Bredt & Snyder, 1992). The effects of these retrograde messengers on presynaptic functions probably involve a modification of the enzymatic processes regulating neurotransmitter release. For example, it is believed that arachidonic acid acts by activating phosphorylation reactions in the presynaptic terminals that are linked to the regulation of transmitter release (see below). Similarly, NO has been shown to stimulate the synthesis of cyclic GMP and to increase neurotransmitter release. In general, the synthesis of both of these retrograde messengers involves the enzymatic cascades discussed above and therefore reflects the local computation of several postsynaptic events. However, the two messengers have different properties. Nitric oxide has a very brief half-life (a few seconds) and is likely to have a limited diffusion range, whereas arachidonic acid has a longer half-life and is likely to have a wider diffusion range. Moreover, there are some uncertainties concerning the types of cells capable of producing NO as most studies have shown a limited distribution of nitric oxide synthases in the CNS. In contrast, arachidonic acid can be produced by a variety of neurons in the CNS. Thus, more work is needed to determine the exact role of

these messengers in neuronal function and in the regulation of synaptic plasticity. Nonetheless, recent studies implicate both arachidonic acid and NO in hippocampal LTP induction (Bliss et al., 1990; Schuman & Madison, 1991, 1994).

Mechanisms Regulating Transmitter Release

Despite intense investigation, the detailed mechanisms underlying neurotransmitter release are not yet understood. An ongoing debate has divided researchers who support the hypothesis that exocytosis of synaptic vesicles accounts for the quantal nature of transmitter release (De Camilli & Jahn, 1990) and those who argue against such a hypothesis and suggest the existence of specialized molecules, mediatophores, that play a critical role in the release process (Israel & Morel, 1990). Nevertheless, several mechanisms that regulate transmitter release have been described. Kandel and colleagues have performed a series of elegant experiments in the sea snail, *Aplysia californica,* to demonstrate an activity-dependent modulation of transmitter release at sensory synapses (Kandel, 1982). Specifically, they have demonstrated that phosphorylation of potassium channels, which regulates the duration of depolarization exhibited by presynaptic terminals invaded by an action potential, regulates the amount of transmitter release at synapses involved in nonassociative habituation and sensitization of gill withdrawal. Their model, which readily accounts for short-term regulation of transmitter release, has been further elaborated to incorporate links between second messengers and the transcription apparatus of the cell (Mayford, Barzilai, Keller, Schacher, & Kandel, 1992). This could account for the long-term modifications of transmitter release that would be required to subserve long-term changes in synaptic efficacy. Greengard and his collaborators have followed a separate line of investigation to establish that another enzymatic cascade regulates the properties of transmitter release. In their model, phosphorylation of a protein associated with synaptic vesicles regulates the pool of vesicles that can participate in transmitter release (Sudhof, Czernik, Kao, Takei, Johnston, Horiuchi, Wagner, Perin, De Camilli, & Greengard, 1989). In both models, however, it is important to stress that the mechanisms involved in the regulation of transmitter release belong to the general class of enzymatic cascades described above and thus exhibit the appropriate features of integrating devices.

Mechanisms Regulating Transmitter Responsiveness

A variety of mechanisms regulate the postsynaptic responses elicited by neurotransmitters. In general, two categories of mechanisms have been described, one affecting the properties of ionotropic receptors and another, applicable to the specialized case of spine contacts, regulating the transfer of electrical signals from the spine head to the dendritic shaft. The responsiveness of ionotropic receptors reflects several parameters including the affinity of the receptor for neurotransmitter and the mean open time and conductance of the channel, to name a few. Modifications of any of these receptor parameters have been shown (at least in simulation models) to change postsynaptic responses to neurotransmitters (Ambros-Ingerson & Lynch, 1993; Heidmann & Changeux, 1982). Likewise, computational models have indicated that structural modifications of the dendritic spine (e.g., spine shaft diameter) can similarly influence postsynaptic responsiveness to transmitter (Wilson, 1988).

The molecular characterization of ionotropic receptors has indicated that they all exhibit consensus sequences for phosphorylation reactions. In several cases, it has been directly shown that receptor phosphorylation modifies the functional properties of the receptors (Greengard, Jen, Nairn, & Stevens, 1991; Huganir & Greengard, 1990). Furthermore, regulation of receptor functional properties has also been shown to occur through interaction with cytoskeletal elements such as actin filaments in the case of NMDA receptors (Rosenmund & Westbrook, 1993). Thus, enzymatic cascades involving phosphorylation reactions are linked to the function of ionotropic receptors. It is also likely that other enzymatic cascades, not necessarily limited to phosphorylation reactions, but associated with the regulation of membrane structures, also influence the functional properties of ionotropic receptors. Similarly, the transfer of electrical signals from spine head to dendritic shaft depends on structural and functional properties of elements constituting the dendritic spines and could be subjected to regulatory mechanisms mediated by enzymatic cascades (Wilson, 1988).

Mechanisms Involved in LTP Expression

Studies of the mechanisms underlying LTP of synaptic transmission in hippocampal circuits perfectly illustrate the general principles discussed above. As was described earlier, LTP is triggered by the activation of postsynaptic NMDA receptors. NMDA

receptors are regulated by allosteric factors (e.g., Mg^{2+}, glycine, polyamines, Zn^{2+}), voltage (i.e., voltage-dependent Mg^{2+} blockade of the channel), and phosphorylation reactions (e.g., protein kinase C phosphorylation; Ben-Ari, Aniksztejn, & Bregetovski, 1992; Thomson, 1990). Activation of NMDA receptors under conditions of correlated pre- and postsynaptic activity results in an influx of calcium in postsynaptic structures and a consequent triggering of enzymatic cascades and immediate early genes (IEGs) encoding transcriptional factors (Cole, Saffen, Baraban, & Worley, 1989; Wisden, Errington, Williams, Dunnett, Waters, Hitchcock, Evan, Bliss, & Hunt, 1990). Thus, the NMDA receptor represents an integrating device which incorporates presynaptic information (glutamate release) and postsynaptic information (membrane potential, levels of second messengers, cytoskeletal conformation).

In contrast to the mechanisms involved early in LTP induction, the nature and location of the modifications responsible for the long-term expression and maintenance of synaptic efficacy are still a matter of controversy (Baudry & Davis, 1991). For some, postsynaptic activation of enzymatic cascades produces the synthesis and release of retrograde messengers which, by mechanisms discussed above, diffuse to the presynaptic terminals and interact with presynaptic enzymatic cascades to produce lasting changes in transmitter release (Bekkers & Stevens, 1991; Bliss et al., 1990; Malinow, 1991; Malgaroli & Tsien, 1992; Malinow & Tsien, 1990; O'Dell et al., 1991; Schuman & Madison, 1991, 1994). Conversely, postsynaptic activation of enzymatic cascades leads to long-lasting alterations in the properties of AMPA receptors, a process that could conceivably enhance postsynaptic responsiveness to released transmitter. Recent results have provided strong support for this latter hypothesis. In particular, the waveform of excitatory postsynaptic potentials is significantly modified following LTP induction, an effect which is more likely to reflect a modification of receptors than of transmitter release (Ambros-Ingerson et al., 1991). Moreover, the effects of compounds which directly interact with postsynaptic AMPA receptors are different at potentiated synapses compared to control synapses (Shahi & Baudry, 1992; Staubli et al., 1990a; Staubli et al., 1992; Xiao et al., 1991). Finally, agonist binding to postsynaptic AMPA receptors is selectively modified following LTP induction, and the increase in binding is positively correlated with the magnitude of LTP (Maren et al., 1993b; Tocco et al., 1992). Again, it is important to stress that the long duration of LTP which has been observed in behaving animals implies that a complex enzymatic cascade or set of cascades is involved to produce a long-lasting modification of synaptic efficacy.

Mechanisms Involved in LTD Expression

At present, the best understood example of LTD is certainly the decreased responsiveness of cerebellar Purkinje cells to parallel fiber stimulation following the simultaneous activation of parallel and climbing fibers. In contrast to LTP, the triggering mechanism for LTD involves the activation of metabotropic glutamate receptors. Nevertheless, LTD induction, like LTP, involves postsynaptic enzymatic cascades that integrate information related to the timing of two separate inputs (climbing fiber and parallel fiber input). These cascades involve second messenger systems and phosphorylation reactions that ultimately produce a modification in the properties of ionotropic glutamate (AMPA) receptors. Possibly, these processes are similar to those that produce a down-regulation of other transmembrane receptors (Carpentier, 1992). Whether similar types of LTD are observed in hippocampal and cortical pathways remains a controversial subject (but for a recent demonstration of NMDA receptor-dependent LTD in hippocampus see Mulkey & Malenka, 1992). And even though it is likely that some forms of LTD do exist in circuits other than those in the cerebellum, the exact mechanisms may well be different (Artola et al., 1990; Artola & Singer, 1993). Nevertheless, it is clear that they will exhibit the features that were discussed above, i.e. integrating devices and enzymatic cascades.

SYNAPTIC PLASTICITY, LEARNING, AND MEMORY

How does the understanding of cellular and molecular mechanisms underlying synaptic plasticity bring us closer to an understanding of the mechanisms underlying learning and memory? Answers to this question are probably best illustrated by again examining the example of LTP in the hippocampus. First, the identification of the role of NMDA receptors in LTP induction has provided a molecular explanation for the links between LTP and the theta rhythm, a prominent rhythm in the EEG of animals engaged in exploratory behavior (Vanderwolf, 1969). The relationship between theta rhythm and learning and memory has been known for decades (Klemm, 1976; Landfield, 1976) and the elucidation of the molecular and cellular mecha-

nisms of LTP has now provided an explanation for the relationship between global events occurring during information processing and local storage of information. Second, understanding the cellular and molecular mechanisms of LTP has provided not only new interpretations for results of pharmacological studies concerning memory (Baudry & Massicotte, 1992), but also new tools (e.g., receptor binding techniques) to probe neural systems for LTP-related changes and new pharmacological compounds to analyze the role for LTP in information processing and storage. It is now possible to make some testable predictions concerning the potential effects of drugs on memory processes (e.g., Granger, Staubli, Davis, Perez, Nilsson, Rogers, & Lynch, 1993; Staubli, Rogers, & Lynch, 1994). Finally, computer simulations of biologically relevant neural networks have begun to incorporate biologically relevant parameters based on LTP induction rules (Ekeberg, Wallen, Lansner, Traven, Brodin, & Grillner, 1991; Granger, Whitson, Larson, & Lynch, 1994; Willshaw & Buckingham, 1990). These models have the potential to become powerful tools to link neurobiology and cognitive sciences.

Hippocampal LTP and Memory

Although it is tempting to take for granted a role for LTP in learning and memory, one must recognize that it might be an impossible task to obtain direct supporting evidence. Nonetheless, several pieces of evidence argue that LTP is involved in behavioral learning and memory. As mentioned earlier, hippocampal LTP exhibits many properties that are characteristic of learning and memory such as rapid formation, long duration, associativity, and cooperativity (Bliss & Collingridge, 1993; Teyler & DiScenna, 1984) and is induced by patterns of stimulation that mimic endogenous theta rhythm (Larson & Lynch, 1986). In addition to these studies, there are reports of LTP-like changes in hippocampal electrophysiology during associative learning (Roman, Staubli, & Lynch, 1987; Skelton, Scarth, Wilkie, Miller, & Phillips, 1987; Weisz, Clark, & Thompson, 1984) and exploration (Sharp, McNaughton, & Barnes, 1989; Green, McNaughton, & Barnes, 1990).[8] Further evidence supporting a role for LTP in learning comes from studies using electrical stimulation to saturate LTP before training: in spatial tasks hippocampal LTP induction impairs learning (McNaughton, Barnes, Rao, Baldwin, & Rasmussen, 1986; Castro, Silbert, McNaughton, & Barnes, 1989), whereas in nonspatial tasks it facilitates learning (Berger, 1984; Doyère & Laroche, 1992; Laroche, Doyère, & Bloch, 1989).[9] Behavioral manipulations that impair LTP induction, such as stress (Diamond, Bennett, Stevens, Wilson, & Rose, 1990; Shors, Seib, & Levine, & Thompson, 1989), produce impairments in hippocampus-dependent spatial learning (Shors & Dryver, 1992). All of these findings are suggestive of a role for LTP in learning, but considerable work is still required to obtain direct evidence for endogenous LTP in behaving animals.

Pharmacological analyses of LTP have proved to be very useful in bolstering the link between LTP and learning. Perhaps the strongest evidence for a role of LTP in learning and memory comes from studies using pharmacological antagonists of the NMDA receptor. Many laboratories have now reported that NMDA receptor antagonists impair learning when applied either systemically (Robinson, Crooks, Shinkman, & Gallagher, 1989; Shapiro & Caramanos, 1990), intracranially (Kim, DeCola, Landeira-Fernandez, & Fanselow, 1991; Morris et al., 1986; Staubli, Thibault, DiLorenzo, & Lynch, 1989), or locally to specific brain structures (Izquierdo, da Cunha, Rosat, Jerusalinsky, Ferreira, & Medina, 1992; Jerusalinsky, Ferreira, Walz, da Silva, Bianchin, Ruschel, Zanatta, Medina, & Izquierdo, 1992; Miserendino, Sananes, Melia, & Davis, 1990; Young, Bohenek, and Fanselow, 1994); the performance of learned responses is not affected by NMDA receptor antagonists (e.g., Kim et al., 1991). Antagonists of the AMPA (Jerusalinsky et al., 1992) and metabotropic (Riedel, Wetzel, & Reymann, 1994) glutamate receptors have also been shown to impair learning. In addition, pharmacological blockade of AMPA receptors abolishes the expression of learned responses in a number of paradigms (Bianchin, Walz, Ruschel, Zanatta, da Silva, Bueno e Silva, Paczko, Medina, & Izquierdo, 1993; Falls, Miserendino, & Davis, 1992; Izquierdo, Bianchin, Silva, Zanatta, Walz, Ruschel, da Silva, Paczko, & Medina, 1993; Izquierdo, da Silva, Bueno e Silva, Quillfeldt, & Medina, 1993; Kim, Campeau,

[8] A recent report indicates that the changes in brain temperature that accompany exploration may be responsible for the increases in hippocampal responses observed by Sharp et al. (1989) and Green et al. (1990) (Moser, Mathiesen, & Andersen, 1993). The relevance of these exploration-related increases in hippocampal responses to memory are therefore questionable. See Eichenbaum & Otto (1993) for an optimistic account of the impact of these studies.

[9] There have been several recent failures to replicate Castro et al. (1989), raising doubts about its validity (e.g., Korol, Abel, Church, Barnes, & McNaughton, 1993). It is nonetheless clear that LTP saturation can have an impact on some forms of learning (e.g., Berger, 1984).

Falls, & Davis, 1993) and drugs that enhance AMPA receptor function improve learning and memory (Granger et al., 1993; Staubli et al., 1994). These studies suggest a role for postsynaptic AMPA receptors in the expression of memory.

Further evidence for a role for postsynaptic AMPA receptors in learning and memory comes from studies indicating that both LTP and classical conditioning are accompanied by similar changes in the binding properties of AMPA receptors in the hippocampus (Maren et al., 1993b; Tocco et al., 1992; Tocco, Devgan, Hauge, Weiss, Baudry, & Thompson, 1991). In addition, certain hippocampus-dependent behaviors, such as emergence neophobia, are correlated with LTP (Maren, Patel, Thompson, & Mitchell, 1993a) and hippocampal glutamate receptor binding (Keller, Borghese, Carrer, & Ramirez, 1992; Maren, Tocco, Chavanne, Baudry, Thompson, & Mitchell, 1994c). Similarly, age differences in hippocampal LTP parallel both age differences in spatial learning (Barnes, 1979) and hippocampal glutamate receptors (Clark, Magnusson, & Cotman, 1992; Pelleymounter, Beatty, & Gallagher, 1990). Collectively, these studies indicate that LTP and the AMPA receptors that express it are critically involved in memory expression.

The view that LTP is involved in mediating learning and memory is also supported by a number of studies showing that inhibitors of PKC and CamKII, enzymes thought to be involved in the induction of hippocampal LTP, produce learning impairments in a number of behavioral paradigms including peck avoidance in chicks (Burchuladze, Potter, & Rose, 1990; Serrano, Benistan, Oxonian, Rodriguez, Rosenzweig, & Bennett, 1994) and avoidance learning in rats (Jerusalinsky, Quillfeldt, Walz, da Silva, Medina, & Izquierdo, 1994). Moreover, discrimination learning in rats is associated with a redistribution of hippocampal PKC (Olds, Golski, McPhie, Olton, Mishkin, & Alkon, 1990). Recent developments in molecular biology have yielded exciting new techniques to "knockout" the expression of genes thought to underlie LTP, thereby expanding the molecular realm for manipulating synaptic plasticity mechanisms. Recently, mice deficient in genes coding for enzymes involved in LTP induction (e.g., PKC and CamKII) have been found to exhibit learning impairments (Abelovich, Chen, Goda, Silva, Stevens, & Tonegawa, 1993; Abelovich, Paylor, Chen, Kim, Wehner, & Tonegawa, 1993; Grant, O'Dell, Karl, Stein, Soriano, & Kandel, 1992; Silva, Stevens, Tonegawa, & Wang, 1992). Unfortunately, it is difficult to dissociate learning from performance deficits in these mice, and their considerable developmental deficiencies suggest that performance factors might account for these results. Moreover, gene knockout cannot be applied to specific brain structures, so it is subject to the same criticisms directed at behavioral studies using systemic administration of pharmacological agents. Nonetheless, the knockout strategy should prove to be a powerful one in further elucidating the biochemical mechanisms of synaptic plasticity in the mammalian brain and their relationship to behavior. In view of recent reports of specific IEG induction following LTP induction (e.g., Worley, Bhat, Baraban, Erickson, McNaughton, & Barnes, 1993; but see Schreiber, Maren, Tocco, Shors, & Thompson, 1991) and learning (Campeau, Hayward, Hope, Rosen, Nestler, & Davis, 1991; Pezzone, Lee, Hoffman, & Rabin, 1992), IEG knockouts may be a profitable avenue for future studies of the relationship of synaptic plasticity to learning and memory.

It is apparent from the foregoing discussion that multidisciplinary studies bridging behavior, systems neurophysiology, receptor biochemistry, and molecular genetics will be the wave of the future to enhance the connection between LTP and memory. For example, we have recently used such a multidisciplinary approach to bridge hippocampal glutamate receptor binding, LTP, and learning. Specifically, we found that acute water deprivation increases hippocampal AMPA receptor binding (S. Maren, S. Standley, C. S. Aquino, & M. Baudry, unpublished observations), elevates hippocampal LTP expression and theta rhythm (Maren, DeCola, Swain, Fanselow, & Thompson, 1994b), and markedly facilitates the acquisition of Pavlovian fear conditioning in rats (Maren, DeCola, & Fanselow, 1994a; Maren et al., 1994b). This sort of multidisciplinary analysis has many advantages because it permits hypothesis testing both within and between a number of levels of biological organization and provides numerous opportunities for establishing convergent validity with other paradigms.

Cerebellar LTD and Memory

Cerebellar LTD has long been proposed as a mechanism for various forms of motor learning mediated by the cerebellum. For example, Ito and colleagues have proposed that cerebellar LTD mediates adaptation of the vestibulo-ocular reflex, a simple form of learning mediated by cerebellar circuits. Furthermore, Thompson and colleagues have argued that learned associations formed during classical eyeblink conditioning in rabbits reside in the cerebellum, possibly as a result of LTD mechanisms

in cerebellar cortex (Thompson, 1990). However, the lack of specific manipulations for preventing LTD induction has hindered studies of its relationship to learning and therefore there is considerably less literature in this area than there is for LTP. Nonetheless, in recent years considerable progress has been made in elaborating the synaptic and molecular mechanisms of LTD in the cerebellum and this should provide the opportunity for the sorts of studies that have been applied to the behavioral analysis of LTP. For example, it has recently been reported that NO synthesis inhibitors, which impair cerebellar LTD induction, impair eyeblink conditioning in rabbits (Chapman, Atkins, Allen, Haley, & Steinmetz, 1992). Interestingly, these same inhibitors have no effect on learning mediated by the hippocampus (Barnes, McNaughton, Bredt, Ferris, & Snyder, 1992), suggesting that NO has a limited role in hippocampal synaptic plasticity. Nonetheless, these studies are consistent with a role for NO-dependent LTD in various forms of cerebellum-dependent motor learning.

Pharmacological Modulation of Learning and Memory

In addition to glutamate receptor antagonists, a variety of pharmacological compounds have been shown to influence learning and memory processes. Unfortunately, it is often extremely difficult to identify the mechanisms of action of the compounds, the neural loci where the modulation takes place, and the specificity of the effects. However, an understanding of the molecular and cellular mechanisms underlying various forms of synaptic plasticity, such as LTP, provides a framework to evaluate the effects of specific drugs on learning and memory. For example, in view of the role of cholinergic neurons in the generation of the theta rhythm (Bland, 1986), the effects of drugs interacting with cholinergic neurotransmitter systems can now be interpreted in relation to hippocampal theta rhythm and LTP induction. Similarly, the effects on learning and memory of drugs acting on GABA receptors (such as benzodiazepines and β-carbolines) can be accounted for on the basis of their effects on LTP induction mechanisms (Baudry & Massicotte, 1992). While it is fruitful to use knowledge of cellular mechanisms of synaptic plasticity to generate new interpretations for old experiments, it is probably more exciting to use it to develop new pharmacological tools that would be more specific and selective for biochemical systems involved in learning. In this regard, several attempts have been made to develop cognitive enhancers based on the properties of synaptic plasticity mechanisms. One approach has been directed toward developing pharmacological agents that facilitate activation of NMDA receptors. However, the success of this approach has been relatively limited thus far, although a glycine analog, D-cycloserine (an allosteric modulator of the NMDA receptor), has been reported to reverse the amnestic effects of scopolamine (a cholinergic antagonist; Fishkin, Ince, Carlezon, & Dunn, 1993; Jones, Wesnes, & Kirby, 1991) in rats and to facilitate learning in rabbits (Thompson, Moskal, & Disterhoft, 1992). Another approach would be to develop compounds that modulate the properties of AMPA receptors. For example, treatment of rats with phosphatidylserine (PS), a phospholipid which increases the affinity of AMPA receptors for agonists (Baudry, Massicotte, & Hauge, 1991), has been reported to improve cognitive impairments associated with aging (Corwin, Dean, Bartus, Rotrosen, & Watkins, 1985; Drago, Canonico, & Scapagnini, 1981; Zanotti, Aporti, Toffano & Valzelli, 1984). This suggests that agents capable of allosteric modifications of AMPA receptors could be used as cognitive enhancers, a prediction that has recently been verified (Granger et al., 1993; Staubli et al., 1994). Looking beyond postsynaptic receptors, a better understanding of the enzymatic cascades involved in LTP might provide more selective ways of increasing synaptic efficacy. In particular, it might be interesting to increase synaptic efficacy under conditions which would normally remain subthreshold for triggering the enzymatic cascades.

Long-Term Synaptic Plasticity in Artificial Neuronal Networks

Synaptic modification rules similar to those found in hippocampal LTP and cerebellar LTD have been implemented in artificial neuronal networks designed to model hippocampal and cerebellar function, respectively. Although these models are still in their infancy, they have already proved to be powerful tools for understanding the computational and "cognitive" properties of certain types of network designs and rules. Thus, networks with plasticity rules derived from hippocampal LTP have been shown to produce an optimal classification of input signals and to have a very large storage capacity (Ambros-Ingerson, Granger, & Lynch, 1990; Granger & Lynch, 1991; Granger et al., 1994). Similarly, networks designed according to cerebellar circuitry and plasticity exhibit properties of complex motor learning and adaptation (Chapeau-Blondeau

& Chauvet, 1991). The next generation of artificial neuronal networks will have to incorporate more biological features in order to reproduce more sophisticated performance of the neural networks they intend to stimulate. In particular, more detailed information concerning the mechanisms of receptor activation, receptor regulation, second messenger signalling will have to be incorporated to understand the consequences of cellular responses that are measured in seconds and minutes instead of milliseconds. There is no doubt that this kind of continuous updating of neuronal responses is involved in the continuous nature of information processing and storage.

CONCLUSIONS

Clearly, much has been learned about brain mechanisms of information processing and storage since Hebb's original concept of a modifiable cell assembly. One can even hope that within a few years, the intimate details of the neurobiological processes involved in learning and memory will be fully understood. Already, it is possible to explain many simple forms of learning and memory in terms of neural circuitries and cellular mechanisms. In particular, several forms of classical conditioning are now understood from the molecular to the behavioral level (e.g., Alkon, 1987). Similarly, more complex cognitive operations, although not explainable with the same degree of precision, can now be subjected to testable experimental hypotheses. What emerges from the multitude of studies directed toward understanding the phenomenon of learning and memory is the necessity to integrate information concerning cellular and molecular mechanisms. As we have seen, the voltage-dependency of a single molecular entity, the NMDA receptor, imparts clearly identifiable properties to the learning process. Moreover, molecular studies of synaptic plasticity have provided important tools (e.g., glutamate receptor binding) to examine synaptic correlates of LTP during learning. However, there is still much to be learned about the molecular nature of learning and memory processes; for example, the identification of several NMDA receptor-independent forms of synaptic plasticity (e.g., Grover & Teyler, 1990) greatly enlarges the domain of molecular mechanisms underlying memory formation. And although further molecular analyses of synaptic plasticity are critical, a full understanding of the mechanisms of learning and memory will only be accomplished through an interdisciplinary effort by researchers operating at a number of levels of biological organization.

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